Remarks/Arguments

The present amendment, without prejudice to future prosecution: amends claims 1, 4-6, 8, 33, 36, 38, 47, 48, 53 and 54; and cancels claims 3 and 37. The provided amendments are intended to facilitate prosecution of the present applicant and are not an admission that applicants agree with any provided rejection.

Claims 1 and 8 were amended to refer to "94% identical", rather then "90% identical". The amendment to claim 1 incorporates the percent identical description previously provided in dependant claim 3. The amendment to claim 8 incorporates the percent identical description previously provided in dependant claim 37.

The amendments to claims 5, 6, 47, 48, 53 and 54 provide editorial revisions taking into account the examiner's suggestions and remarks. The provided editorial revisions do not alter the claim scope.

The dependency of claims 4, 33, 36 and 38 was revised. The change in dependency does not change the scope of the claims.

Applicants thank the examiner for discussing the finality of the prior rejection on December 17, 2009. As noted in the Examiner Interview Summary, applicants and the examiner disagreed as to the extent of the prior amendments. Applicants indicated that the claims were not significantly amended and that some claims, such as claim 33, provided only a very minor editorial revision. The examiner indicated that the amendments changed the scope of the claims necessitating a written description rejection. Applicants pointed out that the descriptions which were now the basis for the written description rejection were present in the previously pending claims.

Subsequent to the interview, applicants petitioned for removal of the final rejection. The petition was denied.

It is respectfully submitted that the denial of the petition fails to take into account dependent claims, such as claims 33-35, whose scope was not altered by the prior amendment. Applicants request reconsideration of the finality of the prior rejection.

Applicants request entry of the enclosed amendment to clams, and that the provided rejections and objections be removed. The different rejections and objections provided in the prior office action are discussed below.

35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1, 3, 4, 7-9, 33-35, 37-44, 47, 49-51 and 53 stand rejected as allegedly lacking written description. The patent office argues each of polypeptide variants covered by the claims are required to provide protection against homologous or heterologous *S. aureus* in a human or non-human host, and notes that reference to patient in claim 8 and human in claims 38, 40, 42, 44 encompasses immunosufficient, immunodeficient and immunocompromised patients. The examiner argues SEQ ID NO: 1 is the only polypeptide tested in the application that is covered by the claims and shown to be protective; the challenge strain for protection is not disclosed; a polypeptide of amino acids 82-486 is not protective, but has an amino acid sequence identity of 90.58 % to SEQ ID NO: 1, which allegedly indicates the criticality of retaining all of the amino acids residues of SEQ ID NO: 1 to provide protection; and the SEQ ID NO: 28 results are not relevant because SEQ ID NO: 28 is a full-length sequence, which does not fall within the scope of the claimed genus.

The examiner cites to references concerning *spa* and capsular polysaccharides (von Eiff *et. al.* (*Diagn. Microbiol. Infect. Dis.* 58:297-302, 2007)) and the potential affect of an amino acid alteration on peptide-antibody interaction. Colman P.M. (*Research Immunol.* 145:33-36, 1994), McGuiness *et al.,* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al*., (*Lancet* 337:514-517, March 1991) are cited for the position that a change of a single amino acid can disrupt antibody-polypeptide binding. The rejection is respectfully traversed.

It is respectfully submitted the rejection: (1) improperly characterizes and discounts the data provided in the application; (2) improperly requires the immunogen described in the claims to provide protective immunity against every possible *S. aureus* in a non-human or human host, and for claims referencing a patient requires the immunogen to be effective against immunosufficient, immunodeficient and immunocompromised patients; and (3) is improperly based on the possibility of an amino acid alteration disrupting an antibody-protein interaction without taking into account the likelihood such a disruption would occur within a polypeptide epitope and would render the polypeptide no longer protective.

The data and guidance provided in the present application reasonably conveys to those skilled in the art that applicants were in possession of claimed protective immunogens, when the

application was filed. To meet the written description requirement "applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention." In re Alton,* 37 USPQ2d 1578, 1581, 76 F.3d 1168, 1172 (Fed. Cir. 1996), quoting *Vas-Cath Inc. v. Mahurkar* 935 F.2d 1563-1564, 19 USPQ 1111, 1117 (Fed. Cir. 1991).

(1) The Rejection Improperly Characterizes and Discounts the Data Provided in the Application

The data provided in the application clearly demonstrates that applicants were in possession of the protective immunogens covered in the claims. Different examples are provided in the application including: Example 3, which provides protection data using different polypeptides and which the application indicates *S. aureus* strain Becker was used as the challenge strain; Example 6 illustrating the use of a full-length construct to provide protection against different clinical isolates; and Example 16 illustrating the use of different polypeptides to provide protection.

The provided protection data was generated employing different constructs such as SEQ ID NO: 3, SEQ ID NO: 4 containing a carboxyl His-Tag, SEQ ID NO: 5 containing a carboxyl His-Tag, and SEQ ID NO: 28 (corresponding to a full-length sequence with a His-Tag). SEQ ID NOs: 1 and 5 provide a protective region corresponding to an ORF0657nI region. SEQ ID NOs: 3 and 4 provide a protective region corresponding to an ORF0675nH region. SEQ ID NOs: 3, 4, and 5 are covered by at least independent claims 1 and 8.

Appendix A, attached hereto, is a sequence comparison of SEQ ID NOs: 1, 3, 4, 5 and 28. The leader sequence and the sortase cleavage site are noted in the sequence comparison. The sequence comparison also highlights amino acids at a couple of variable amino acids present in SEQ ID NOs: 1, 3, 4, 5 and 28. Figures 2A-2E, which are present in the filed application, provides a sequence comparison of different ORF0657n sequences across the ORF0657nH region and includes SEQ ID NOs: 1, 3, 4, and 5.

The Appendix A sequence comparison provides a useful illustration of the SEQ ID NO: 28 region expected to be involved in producing protective immunity. Both the leader sequence and LPXTG are cleavage points during cellular processing. (See, for example, the present application at page 19, lines 9-18). Cleavage at the LPXTG motif is indicated in Appendix A by

reference to the "Sortase Cleavage Site". The SEQ ID NO: 28 region expected to be present in the cell wall corresponds approximately to the ORF0657nH region of SEQ ID NO: 3. The expected SEQ ID NO: 28 cell wall region has four additional carboxyl amino acid than SEQ ID NO: 3.

(1)(A) Example 3 Strain Becker Data

Example 3 illustrates the ability of polypeptides of SEQ ID NOs: 4, 5 and 28 to provide protection against *S. aureus* strain Becker. (The present application at pages 26-27.) As noted above, SEQ ID NOs: 4 and 5 employed in the Example 3 also contained a His-Tag. The results of Example 3 are provided in Figures 3A, 3B, and 3C. The brief description of Figures 3A, 3B, and 3C refer to the use of strain Becker. (The present application at page 5, lines 16-23.)

The full-length ORF0657n *S. aureus* strain Becker contains a 95% sequence identity to the full-length ORF0657n COL sequence (SEQ ID NO: 2). (See the present application at page 29, Table 3.) SEQ ID NOs: 1, 3, 4, 5 and 28 are based on the COL sequence. (See, for example, the present application at page 8, lines 7-11 and 16-18.)

SEQ ID NOs: 4 and 5 are within the scope of at least independent claims 1 and 8. The ability of immunogens containing these sequences to provide protective immunity against *S. aureus* strain Becker clearly demonstrates that the exact sequence employed as a protective immunogen in the example is not critical.

Based on random chance, one of ordinary skill in art would expect the differences between *S. aureus* strain Becker and COL to be located in different regions including the OFR0657nI and ORF0657nH regions. Figures 2A-2E confirm such expectation by providing evidence that differences among different ORF0657n present in different strains occur in different locations including the OFR0657nI region and the ORF0657nH region.

A sequence comparison between the strain Becker ORF0657n, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 is attached hereto as Appendix B. The sequence comparison confirms the evidence provided in the application, and what would be expected by one skilled in the art, concerning the presence of different alterations between COL and Becker being located in different regions.

The ability of SEQ ID NOs: 4 and 5 to provide protective immunity against the heterologous *S. aureus* strain Becker provides important evidence that alterations to the sequences used in the application could be made and resulting immunogens would be protective. For example, the skilled artisan could expect the naturally occurring sequence present in the *S. aureus* Becker strain to provide protective immunity against at least strain Becker. Such an expectation of protection is based on, for example, a polypeptide providing a ORF0657nI or ORF0657nH region based on strain Becker having a greater degree of homology to strain Becker ORF0657n than SEQ ID NOs: 4 or 5.

(1)(B) Example 6 - Data using Full-Length Constructs on Different Clinical Isolates

The present application illustrates the ability of the polypeptide of SEQ ID NO: 28 to provide protection against different *S. aureus* strains. (The present application at Example 6, page 29, Figures 4A-4H, and brief description of the figures provided on page 5, lines 23-31.) The ability of a full-length ORF0657n to provide protective immunity against different clinical isolates confirms the expectation that alterations can be made to a reference sequence provided in one or more claims, where the resulting polypeptide retains its protective ability.

The prior office action dismisses the SEQ ID NO: 28 data based on SEQ ID NO: 28 not being within the scope of the claims. It is respectfully submitted that the data with SEQ ID NO: 28 is very relevant to the claims and provides important information to one of ordinary skill in art concerning the ability of different polypeptides to provide protective immunity.

The relevance of the data is illustrated by reference to Figures 2A-2E and Appendix A. The ORF0657nI region of SEQ ID NO: 1 illustrated in Figures 2A-2E starts at amino acid 3 and runs to the end of SEQ ID NO: 1. The ORF0657nH region of SEQ ID NO: 3 illustrated in Figures 2A-2E goes from amino acid 3 to the end of SEQ ID NO: 3. Figures 2A-2E illustrates examples of differences between SEQ ID NOs: 1 and 3, and different naturally occurring sequences.

Appendix A illustrates the processing sites of ORF0657n that produce a region expected to be present in the *S. aureus* wall. Due to processing of the leader sequence and the sortase cleavage site, a region approximately corresponding to the ORF0657nH is expected to be present.

The portion of SEQ ID NO: 28 expected to be involved in providing protective immunity is that portion generating an immune response against a polypeptide present on the cell wall. For SEQ ID NO: 28, the relevant region corresponds to the SEQ ID NO: 3 ORF0657nH region plus an additional four amino acids, which provides for a sequence identity of 568 amino acids out of 572 amino acids or over 99%.

The ORF0657nI region of SEQ ID NO: 1 also has a significant overlap with the portion of SEQ ID NO: 28 remaining after cellular processing. The overlap contains an exact match of 445 amino acids out of 572. The overlap runs across about 78% of the relevant portion of SEQ ID NO: 28. Example 3, discussed above, illustrates that the ORF0657nI region is sufficient to provide protective immunity.

Figures 4A-4H illustrate the ability of SEQ ID NO: 28 to provide protection against different heterologous clinical isolates designated CL-10, CL-13, CL-30, CL-18 and CL 21. With respect to the Figures 2A-2E sequence alignment: CL-10 corresponds to ID11, CL-13 corresponds to ID19, CL-18 corresponds to ID-18, CL-21 responds to ID-22, and CL30 corresponds to ID24.

The ability of SEQ ID NO: 28 to provide protective immunity against different strains of *S. aureus* provides important evidence that alterations to the sequences used in the application to provide protection could be made, and the resulting polypeptide would not be prevented from providing some protection. Based on the data and guidance provided in the application, the skilled artisan would expect, for example, the naturally occurring ORF0657nI or ORF0657nH region present in the *S. aureus* strain used as a challenge strain, to provide protective immunity against the challenged strain. For example, based on Figures 4A-4H, the corresponding ORF0657nI or ORF0657nH region from CL-10, CL-13, CL-30, CL-18 and CL 21 would at least be expected to provide protection against the homologous strain.

CL-10, CL-13, CL-30, CL-18 and CL 21 are diverse *S. aureus* strains with different degrees of sequence identity to SEQ ID NO: 2. (The present application at pages 28 and 29, Table 3.) CL-10 has a 97% sequence identity to SEQ ID NO: 2, CL-13 has a 99% sequence identity to SEQ ID NO: 2, CL-21 is a methicillin resistant strain with a 94% sequence identity to SEQ ID NO: 2, and CL-30 has a 96% sequence identity to SEQ ID NO: 2. As noted above, claims 1 and 8 were amended to provide for at least 94% identical to a referenced sequence.

(1)(C) Example 16 – Additional Protection Data

Additional protection data using different constructs is provided by Example 16 of the application. (The present application at page 50, line 30 to page 51, line 21.) The results are shown in Figure 10. With respect to Figure 10, ORF0657nH (*E. coli*) corresponds to SEQ ID NO: 4 with a carboxyl His-Tag, ORF0657nI (*E. coli*) corresponds to SEQ ID NO: 5 with a carboxyl His-Tag, ORF0657nC (*E. coli*) corresponds to SEQ ID NO: 28; and ORF0657nH (yeast) correspond to SEQ ID NO: 3. (The present application at page 7, lines 9-14.)

In the experiments illustrated in Figure 10, the polypeptide providing an ORF0657nI region generated a similar level of protection to the polypeptide providing the ORF0657nH region. It is respectfully submitted, that the data provides evidence that ORF0657nH does not contain a critical region beyond that provided by the ORF0657nI region. Such a conclusion is consistent with Example 3 (Figures 3A, 3B, and 3C), illustrating the ability of SEQ ID NO: 5 containing a His-Tag to provide protective immunity (Figure 3C).

While not indicated in the application, the challenge strain employed in Example 16 was *S. aureus* strain Becker.

(2) Use Requirement Imposed by the Patent Office

The patent office is improperly rejecting the claims based on arguments requiring the immunogens to provide protection against every possible *S. aureus* in a non-human or human host, and for claims referencing a patient requiring the immunogen to be effective against immunosufficient, immunodeficient and immunocompromised patients. Such arguments are directed to how a particular polypeptide is used and not whether written description is provided for the claimed immunogen.

As discussed above, the present application illustrates the ability of different immunogens encompassed by the claims to provide protection against different *S. aureus* strains using an animal model. Applicant is not required to illustrate the ability of the claimed polypeptide to provide protective immunity against each and every *S. aureus* in a non-human or human host (including immunosufficient, immunodeficient and immunocompromised patients).

Written description for the pending claims is met, for example, based on the guidance and results provided in the application concerning different immunogens, and their ability to provide protection using a strain of *S. aureus* such as strain Becker or different clinical isolates. Such guidance and results clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date applicants were in possession of the invention.

The claims in question are directed to immunogens and pharmaceutical compositions. How a particular immunogen is used, for example, in an immunosufficient, immunodeficient and immunocompromised patient goes to enablement of a method of use. Given the examples provided in the application using animal models, additional effectiveness in a non-human or human (e.g., immunosufficient, immunodeficient and immunocompromised patient) does not need to be shown. As the rejection appears to be based on enablement for certain uses, applicants note that: "The enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.* 20 USPQ2d 1300, 1304 (Fed. Cir. 1991).

(3) Alterations Affecting Protective Immunity

The rejection fails to present any evidence concerning the likelihood that an alteration within a reference sequence provided in the claims could result in a polypeptide that no longer provides protective immunity. Instead, the rejection is improperly based on the possibility that an amino acid alteration could disrupt an antibody-protein interaction. For example, the rejection fails to indicate the likelihood that an alteration would occur within SEQ ID NO: 1 that prevents SEQ ID NO: 1 from providing protective immunity.

Polypeptides having a high degree of structural similarity are expected to have similar properties. The rejection fails to take into account the structural similarity of the polypeptides recited in the claims and data provided in the application. For example, with respect to SEQ ID NO: 1, the rejection is based on the possibility that an alteration to an amino acid within the 446 amino acids of SEQ ID NO: 1 may impact a protein-antibody interaction, and by altering a particular epitope the polypeptide in no longer protective.

The rejection fails to provide any indication as to why a significant number of polypeptides within the scope of the claims having a sequence structurally related to a protective

polypeptide would not provide protection. The references cited by the examiner to support the rejection concern *spa* and capsular polysaccharides, and the potential effect of an amino acid alteration on peptide-antibody interaction. The ORF0657n target is a polypeptide, not a polysaccharide.

The references concerning antibody-peptide interactions are silent as to the likelihood that a particular alteration would prevent a polypeptide over 410 amino acids in length, shown to be protective, from maintaining its ability to provide protection. Further, even the possibility that some unknown alteration in an amino acid residue may impact a particular protein-antibody interaction, does not necessarily equate to a polypeptide within the scope of the claims losing its ability to provide protective immunity. For example, SEQ ID NO: 1 is 446 amino acids in length and may contain more than one epitope providing a beneficial effect.

The described high degree of structural relationship to a reference polypeptide recited in claims, along with the data in the application, provide more than a mere wish for obtaining a compound able to provide protective immunity. The application provides an expectation that polypeptides covered by the claims will be protective.

35 U.S.C. § 112, Second Paragraph (Definiteness)

(a) and (b) Claims 5 and 53 stand rejected as providing improper antecedent basis in the limitation "the additional 20 amino acids". The examiner indicates the previous limitation in these claims is "up to 20 additional amino acids". Claims 5 and 53 were amended to indicate "the up to 20 additional amino acids". Claim 47 was also amended in the same fashion.

(c) Claim 1 is indicated to be vague and inconsistent based on reference to "where said" and "wherein said". The examiner suggests the use of "wherein". Claim 1 was amended as suggested by the examiner.

(d) The examiner suggests amending line 4 of claim 5, and line 3 of claims 47 and 53, to replace "amino terminus" with "the amino terminus". Claims 5, 47, and 53 were amended as suggested by the examiner.

(e) Claims 5, 47, and 53 are indicated to be vague and indefinite based on reference to "the carboxyl or amino terminus." The examiner indicates it is unclear what element is being

referred to. For example, the examiner inquires if a peptide within SEQ ID NO: 1 or the carboxyl or amino sequence of SEQ ID NO: 1 is being referred to.

The objection is respectfully traversed. Reference to "carboxyl" or "amino" terminus clearly refers to the end region of the referenced sequence and not an addition to an internal sequence.

(f) Claim 8 is indicated to be vague and indefinite based on reference to "provides protective immunity against *S. aureus"* in line 3. The examiner indicates that the claim includes a narrower definition in an earlier part of the claim which indicates the composition is to induce protective immunity in a patient. The examiner inquires whether the protective immunity recited in line 3 of the claim is provided to other than a patient recited in line 2, or to the same patient as in line 2.

The rejection is respectfully traversed. Claim 8 is a composition claim, not a method of use claim. The preamble description of a patient indicates a possible use of the composition and is not a limitation necessitating the use of the immunogen in a patient. Reference to providing protective immunity in the body of the claim against *S. aureus* refers to a property of the composition consistent with the claim preamble. The body of the claim also refers to a pharmaceutically acceptable carrier as part of the composition.

(g) Claim 7 is indicated to be vague and indefinite based on reference to "facilitates polypeptide stability". The examiner indicates that it is unclear the stability of which polypeptide is facilitated. The examiner inquires whether the description refers to a situation where the claimed immunogen is unpurified in association with an unclaimed polypeptide and the stability of the unclaimed polypeptide is facilitated.

The rejection is respectfully traversed. Claim 7 refers to "an amino acid sequence" and goes on to indicate that the one or more additional regions or moieties is covalently joined to "said sequence".

(h) The examiner suggests that the last two lines of claim 7 be amended to replace "enhances the immune response, facilitates purification or facilitates polypeptide stability" with the limitation -- enhancement of immune response, facilitation of purification, or facilitation of . . . stability--. Applicants appreciate the suggestion, but respectively decline. Applicants note that no particular deficiency in the originally present language was alleged.

(i) Claims 3, 4, 6, 9 and 33-54, which depend directly or indirectly from claims 5, 7 or 8 are rejected as allegedly indefinite, because of the indefiniteness identified above in the base claims. The examiner's concerns regarding definiteness of the base claims are addressed above.

Claim Objections

Claims 5, 6, 47, 48, 53 and 54 stand rejected based on the use of the alternative "or" in conjunction with "NOs". The examiner suggests "NOs" be replaced with --NO.--. Claims 5, 6, 47, 48, 53 and 54 were amended along the lines suggested by the examiner, by replacing "NOs:" with --NO:--.

Please charge deposit account 13-2755 for fees due in connection with this amendment. If any time extensions are needed for the timely filing of the present amendment, applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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